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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,975	07/30/2003	James Hunter Boone	TLAB.109338	9513

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/629,975	BOONE ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Amendment Entry

2. Applicants response and amendment filed 31 October 2007 is acknowledged. In the amendment filed therein claims 1, 2, and 6 were modified. Claims 3-5 have been canceled. Currently claims 1, 2 and 6 are pending and under consideration.

3. Rejections and/or objections of record not reiterated herein are withdrawn.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 2 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Claim 2 is rejected because it is dependent on claim 1).

A. Claims 1 and 6 are vague and indefinite because the final comparison step is directed to gastrointestinal inflammation. While the preamble is directed to monitoring inflammatory bowel disease. Accordingly the method and preamble are not clearly directed to the same measurement. In other words, it is not clear as to what the method encompasses. The method lacks a resolution step, which reads back on the preamble of claims. It is suggested that the preamble read on "having inflammatory bowel disease for gastrointestinal inflammation" in order to obviate this rejection. Appropriate correction is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1, 2 and 6 are rejected under 35 U.S.C.103(a) as being unpatentable over Hayes et al. (US Patent #6,358,939 B1) in view of Sreekant Murthy, PhD (Inflammation Research Association, Newsletter, September & December 1999, Vol. 8, No. 3 & 4, pages 1-14) and further in view of Uchida et al. (US Patent #5,552,292).

Hayes et al. teach methods for treating inflammatory bowel disease (IBD) with biologically active vitamin D compounds. See abstract and column 4 lines 41-67, for example. In order to assess/monitor the disease and treatment results, fecal lactoferrin concentrations are measured. See column 20 lines 50-51 and lines 60-61, for example. The assay for lactoferrin employs a two-site ELISA wherein the samples are measured from the linear portion of a log-linear plot at A-450nm. See column 21 lines 36-52. Lactoferrin is measured at two-day interval (first fecal sample at a first time). See column 23 lines 46-47. Calcitriol is begun when the mice are suffering from IBD (treatment). See column 23 lines 47-48. Thereafter, stool samples are obtained at four-day intervals until the mice were euthanized on day 22 (second fecal sample). See column 23 lines 50-54. The results indicated that calcitrol treatment of mice exhibiting symptoms of IBD were reduced as compared to controls. See column 23 lines 58-61. This method is also taught to be useful in monitoring humans with IBD see column 4 lines 34-39 and column 23 line 65 to column 24 line 19.

Although Hayes et al. teach that human IBD patients can be monitored, they do not specifically detect fecal lactoferrin in human patient samples. In other word, Hayes et al. measure fecal samples from mice (DS-induced IBD mouse model) *not* in human samples. For example see Hayes et al. column 19.

However, the prior art teaches that the DS-induced mouse model is useful in studying human IBD. This is supported by the Inflammation Research Association, Newsletter, September & December 1999, Vol. 8, No. 3 & 4, pages 1-14. On page 9 column 3, Sreekant Murthy, PhD mapped out how a dextran sulfate model of mouse colitis histologically and immunohistologically resembles chronic human ulcerative colitis (UC) and human colitis-associated colon cancer. (UC is taught to be IBD in the disclosure on page 2 section 0005). Absent evidence to the contrary the utility of the DS-induced mouse model to study human manifestations is deemed obvious.

In addition, the measurement of human samples for fecal lactoferrin is taught by Uchida et al. Lactoferrin is taught to be a marker for various diseases related to inflammatory gastrointestinal disorders and colon cancer. Column 2 lines 46-59. Lactoferrin was found to be the most stable substance in feces. Column 3 lines 10-11. Specifically, a polyclonal antibody for lactoferrin (DAKOPATT) is employed to measure lactoferrin in inflammatory diarrhea specimens. Column 5 lines 57-61.

The method was performed in an enzyme-linked immunoassay format. A polyclonal antibody against lactoferrin (anti-human lactoferrin antibody) is immobilized onto wells of a 96-well polystyrene micro plate. The plate is contacted with diluted fecal specimen (column 11 lines 31-33 wherein 50Tl of sample is added to 100Tl %1BSA and TBS buffer) and detected with a polyclonal antibody labeled with alkaline phosphatase (anti-human-lactoferrin antibody). See column 11 example 2 and column 5 lines 14-19. The results were correlated to standards prepared with purified lactoferrin. Column 6 lines 13-19.

The assay results were detected at 510/630nm absorbance. Column 11 lines 53-56. Increased levels of lactoferrin were demonstrated to several diseases. See column 12-Results. Uchida et al. teach standard curve comparative analyses (claim 2). Healthy person fecal samples were run and graphed on a curve for comparison to unknown sample sets (standard curve). Column 7 lines 51-64 and column 8 lines 18-29. Kit embodiments are also disclosed. The kit contains antibodies immobilized on a solid phase (micro plate), an enzyme linked antibody, and a chromogene (enzyme substrate for color development). See column 4 lines 1-9 and column 5 lines 36-40.

With respect to endogenous lactoferrin, it is noted that the lactoferrin detected by Uchida et al. were found within the patient (endogenous to the patient) and occurred as a result of disorders.

Normal patients exhibited very small amounts of lactoferrin (0.75 – 2.4Tg/g feces) and Uchida et al. taught that their method could be used in various types of lactoferrin (column 6 lines 58-61). Therefore absent evidence to the contrary Uchida et al. teach the detection of endogenous lactoferrin.

Uchida et al. taught that sample dilution was useful in ensuring that the sample concentrations could be compared to LF quantification curve for accurate measurements within the assay range. Samples are multiplied by a dilution factor of 100. For example, see column 11 lines 56-63. (claims 2 - serial ten fold dilutions until a measured result is obtained). The specification also teaches that the dilution factor can be optimized. See page 10 section 0027. Thus serial dilutions of the sample is mere optimization, taught in the prior art and the instant specification.

Sample dilution is considered obvious since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or working ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to measure *human* lactoferrin fecal samples in the mouse lactoferrin IBD evaluation *assay* of Hayes et al. because Sreekant Murthy PhD taught that the dextran sulfate model of mouse colitis histologically and immunohistologically resembles chronic human ulcerative colitis and human colitis-associated colon cancer (IBD as taught by the disclosure on page 2 section 0005) and Uchida et al. taught that lactoferrin could be measured in human feces. Uchida et al. further taught that lactoferrin is a marker for various diseases related to inflammatory gastrointestinal disorders and colon cancer. Column 2 lines 46-59. Lactoferrin was found to be the most stable substance in human feces. Column 3 lines 10-11.
One of ordinary skill in the art would have been motivated to detect lactoferrin in humans in order to diagnosis, monitor and treat IBD disorders.

II. Claims 1, 2 and 6 are rejected under 35 U.S.C.103(a) as being unpatentable over Hayes et al. (US Patent #6,358,939 B1) in view of Sreekant Murthy, PhD (Inflammation Research Association, Newsletter, September & December 1999, Vol. 8, No. 3 & 4, pages 1-14) and further in view of Sugi et al. (The American Journal of Gastroenterology, Vol.91, No.5, 927-934, 1996).

Hayes et al. teach methods for treating inflammatory bowel disease (IBD) with biologically active vitamin D compounds. See abstract and column 4 lines 41-67, for example. In order to assess/monitor the disease and treatment results, fecal lactoferrin concentrations are measured. See column 20 lines 50-51 and lines 60-61, for example. The assay for lactoferrin employs a two-site ELISA wherein the samples are measured from the linear portion of a log-linear plot at A-450nm. See column 21 lines 36-52. Lactoferrin is measured at two-day interval (first fecal sample at a first time). See column 23 lines 46-47. Calcitriol is begun when the mice are suffering from IBD (treatment). See column 23 lines 47-48. Thereafter, stool samples are obtained at four-day intervals until the mice were euthanized on day 22 (second fecal sample). See column 23 lines 50-54. The results indicated that calcitrol treatment of mice exhibiting symptoms of IBD were reduced as compared to controls. See column 23 lines 58-61. This method is also taught to be useful in monitoring humans with IBD see column 4 lines 34-39 and column 23 line 65 to column 24 line 19.

Although Hayes et al. teach that human IBD patients can be monitored, they do not specifically detect fecal lactoferrin in human patient samples. In other word, Hayes et al. measure fecal samples from mice (DS-induced IBD mouse model) *not* in human samples. For example see Hayes et al. column 19.

However, the prior art teaches that the DS-induced mouse model is useful in studying human IBD. This is supported by the Inflammation Research Association, Newsletter, September & December 1999, Vol. 8, No. 3 & 4, pages 1-14. On page 9 column 3, Sreekant Murthy, PhD mapped out how a dextran sulfate model of mouse colitis histologically and immunohistologically resembles chronic human ulcerative colitis and human colitis-associated colon cancer. (UC is taught to be IBD in the disclosure on page 2 section 0005). Absent evidence to the contrary the utility of the DS-induced mouse model to study human manifestations is deemed obvious.

In addition, Sugi et al. disclose that lactoferrin (LF) levels were elevated in fecal samples of patients with inflammatory bowel disease. The measurement of lactoferrin in human feces was taught to be efficient and lactoferrin was stable in feces. See abstract. The ELISA assay procedure is disclosed on page 928.

Sugi et al. measure samples at different times but does not teach multiple sample collections at different times. The multiple sampling analysis is seen on page 929 in figure 2 for example. LF concentrations are measured at different time intervals, which include 24hours, 48hours, 72hours, and 96hours. The LF concentrations are subsequently compared to each other in figure 2 – A, B, and C (48hrs – 72hours –96 hours are all later than the first 24hour LF detection).

With respect to endogenous lactoferrin, it is noted that the lactoferrin detected by Sugi et al. were found within the patient (endogenous to the patient) and occurred as a result of disorders. Therefore absent evidence to the contrary Sugi et al. teach the detection of endogenous lactoferrin.

Control patients exhibited very small amounts of lactoferrin as compared with UC (ulcerative colitis) and CD (Crohn's disease) patients. For example, see Table I on page 930.

Sugi et al. taught sample dilution from 100- to 10,000-fold with 0.1M tris HCL buffer (reading on claim 2). See page 928 2nd column 3rd paragraph. The instant specification also teaches that the dilution factor can be optimized. See page 10 section 0027. Thus serial dilutions of the sample is mere optimization, taught in the prior art and the instant specification. Sample dilution is considered obvious since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or working ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to measure *human* lactoferrin fecal samples in the mouse lactoferrin IBD treatment/evaluation *assay* of Hayes et al. because Sreekant Murthy PhD taught that the dextran sulfate model of mouse colitis histologically and immunohistologically resembles chronic human ulcerative colitis and human colitis-associated colon cancer. (UC is taught to be IBD in the disclosure on page 2 section 0005). While Sugi et al. taught that lactoferrin could be measured in human feces and related to IBD diseases (CD and UC). Sugi et al. further taught that lactoferrin is an efficient and stable marker. See abstract.

One of ordinary skill in the art would have been motivated to detect lactoferrin in humans in order to diagnosis, monitor and treat IBD disorders.

Response to Arguments

6. Applicant contends that Hayes et al. do not teach human fecal sample measurements. This argument was carefully considered and found persuasive. Accordingly the method of monitoring IBD treatment in mice as taught by Hayes et al. has been combined with Sreekant Murthy, PhD and Uchida et al. *or* Sreekant Murthy, PhD and Sugi et al. to make the claimed invention obvious. Sreekant Murthy teaches that the DS-induced mouse model is useful in studying human IBD. While, Uchida et al. and Sugi et al. teach lactoferrin measurements in human samples.

Applicant argues that the reference to Uchida et al. does not compare the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same person with inflammatory bowel disease. This argument was carefully considered but not found persuasive because Uchida is cited in combination with Hayes et al. Hayes et al. teach this limitation. See column 23 lines 46-60. While a deficiency in a reference may overcome a rejection under 35 USC 103, a reference is not overcome by pointing out that a reference lacks a teaching for which other references are relied. *In re Lyons*, 364 F.2d 1005, 150 USPQ 741, 746 (CCPA 1966).

7. For reasons aforementioned, no claims are allowed.

Remarks

8. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Kwon et al. (Biochemical and Biophysical Research Communications, Vol.337, 2005, pages 647-654) teach dextran sulfate sodium (DSS) induced experimental colitis is mice has been recognized as a useful model for human IBD. See abstract.

B. Sasaki et al. (Free radical Biology & Medicine, Vol.35, No.12, pages 1679-1687, 2003) teach that oral dextran sodium sulfate produces experimental colitis with many features of human inflammatory bowel disease (IBD). See abstract.

C. Tabata et al. (Rinsho Byori, 1997, 45(12), 1201-1203 – Abstract Only) teach that lactoferrin is useful in monitoring inflammatory bowel disease.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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